Gynecol Surg (2012) 9:29–35
DOI 10.1007/s10397-011-0698-0

ORIGINAL ARTICLE

Efficacy of polyethylene glycol adhesion barrier after gynecological laparoscopic surgery

Results of a randomized controlled pilot study

R. P. G. ten Broek · N. Kok-Krant · H. R. Verhoeve · H. van Goor · E. A. Bakkum

Received: 2 May 2011 / Accepted: 11 August 2011 / Published online: 9 September 2011

Abstract Postoperative adhesions are the most frequent complication of peritoneal surgery, causing small bowel obstruction, female infertility and chronic pain. This pilot study assessed the efficacy of a sprayable polyethylene glycol (PEG) barrier in the prevention of de novo adhesions. 16 patients undergoing laparoscopic gynecological surgery were randomly assigned by shuffled sealed envelopes to receive either the adhesion barrier or no adhesion prevention. Incidence and severity of adhesions were scored at eight sites in the pelvis and reassessed by second look laparoscopy. Adhesion prevention was considered successful if no de novo adhesion were found at second look laparoscopy. One patient was excluded before randomization. Nine patients were randomized to treatment and six patients to control group. De novo adhesions were found in 0/9 patients who received the PEG barrier compared to 4/6 without adhesion prevention (0% vs. 67%, P=0.01). Reduction in adhesion score was significantly greater in patients receiving PEG barrier (−2.6 vs. −0.06, P=0.03). Meta-analysis of three randomized trials demonstrated that PEG barrier reduces the incidence of adhesions (odds ratio [OR]= 0.27; 95% CI 0.11–0.67). From this study, PEG barrier seems effective in reducing postoperative formation of de novo adhesions.

R. P. G. ten Broek · H. van Goor
Department of Surgery,
Radboud University Nijmegen Medical Centre,
Nijmegen, The Netherlands

N. Kok-Krant · H. R. Verhoeve · E. A. Bakkum (✉)
Department of Gynaecology and Obstetrics,
Onze Lieve Vrouwe Gasthuis,
P.O. Box 95500, 1090 HM Amsterdam, The Netherlands
e-mail: E.A.Bakkum@olvg.nl

Keywords Tissue adhesions · Laparoscopy · Polyethylene glycol · Hydrogels · Randomized controlled trial

Background

Adhesions develop after gynecological surgery in the pelvic cavity in almost all cases and cause significant morbidity [1]. In a large population-based study of gynecological pelvic surgery, the readmission rate directly or probably related to adhesions was 13.9%, and the introduction of less invasive techniques, such as laparoscopy, did not seem to reduce this adhesion related morbidity [2]. The incidence of adhesive small bowel obstruction (ASBO) after oncologic gynecological surgery is about 11% [3]. Adhesions are the leading cause of secondary female infertility worldwide [4, 5], and an important cause of chronic pelvic pain [6, 7]. In addition, adhesiolysis during reoperation is time-consuming and exposes the patient to the risk of unintended injury such as enterotomy [1, 8].

Adhesion barriers or anti-adhesive agents are needed because refinements in surgical techniques do not seem to be sufficient in reducing adhesion-related morbidity. Several products have come to the market ranging from membranes for selective coverage of injured peritoneal areas to liquids for broad nonspecific coverage. An important drawback of the available membranous adhesions barriers is the difficulty of handling them during laparoscopic procedures. Alternatives to membranes for laparoscopic use are sprays that are easily applied intraperitoneally through trocars at sites that need to be covered. Recently, a sprayable polyethylene glycol (PEG) anti-adhesion barrier was developed for anti-adhesive purposes (SprayGel; Confluent Surgical Inc., Waltham, MA). The PEG adhesion barrier consists of two liquid precursor solutions that quickly react to form a hydrogel after being

sprayed and mixed in the abdomen. One of the precursors contains a small concentration of methylene blue allowing visualization of the area covered and the thickness of the hydrogel layer during laparoscopy. The hydrogel is biodegradable and physically separates the injured peritoneal sites in order to promote adhesion free peritoneal regeneration.

The PEG anti-adhesion spray proved to be effective in rodent and porcine models with 75% reduction of the incidence of adhesions in a rat cecal abrasion model and 60% reduction in a porcine uterine horn model [9, 10]. Four human randomized controlled trials (RCTs) have been performed: two in patients undergoing laparoscopic or open myomectomy and two in patients undergoing loop ileostomy closure [11–14]. No RCT has included patients undergoing laparoscopic surgery alone, and all RCTs included a specific group of patients rather than investigating the various common types of laparoscopic benign gynecological surgery. The use of PEG spray was correlated with a reduction in extend and tenacity of adhesions in these RCTs. However, reductions in adhesion incidence — in contrast to reduction in adhesion extend or tenacity — is particularly important for predicting the value of an anti-adhesive product reducing ASBO and unintended organ injury during adhesiolysis. We undertook a small prospective randomized controlled study to evaluate the PEG spray on adhesion formation in women undergoing common laparoscopic gynecological procedures. In addition, we performed a meta-analysis of reported studies, including the present one, focusing on the efficacy of PEG spray in reducing the incidence of adhesions.

Materials and methods

The study was a randomized single-blinded (patient) study. Patients who were scheduled for laparoscopic treatment of benign gynecologic disease involving ovaries, pelvic sidewalls, fallopian tubes or uterus were assessed for eligibility between September 2002 and March 2004. Inclusion criteria were as follows: age ≥18 years; the patient might benefit from and agrees to return for second look laparoscopy (SLL); and the patient agrees to use contraception until SLL was conducted.

Pregnant and lactating patients were excluded, as well as patients with known or suspected malignancy. Peroperative exclusion criteria were endometriosis classified as stage IV, using the Revised American Society for Reproductive Medicine Classification of Endometriosis scoring system and if complete adhesiolysis was not possible [15].

At the end of index laparoscopic surgery and before removal of all instruments, patients were randomly assigned — via shuffled sealed envelopes — to treatment with PEG or no treatment groups. The PEG barrier was sprayed at all sites of surgical injury with the potential for adhesion formation. SLL was planned to evaluate adhesion formation. The surgeon performing SLL was blinded for the treatment group.

The study protocol was approved by the local Medical Ethical Committee and designed according to the ethical considerations described in the revised version of the Declaration of Helsinki (October 2008, Seoul). All patients gave written informed consent. The study was investigator-driven. PEG was kindly donated by Confluent, Surgical Inc (Waltham, MA, USA). The trial was registered at clinical trials.gov with identifier: NCT01187680.

Adhesion scoring

The incidence of patients with and without any adhesion was assessed in both initial and second look laparoscopies. All surgical procedures were performed by the same surgeons (EB and HV). Adhesions at SLL were classified as de novo adhesions or reformed adhesions. De novo adhesions are adhesions that are newly formed following the first laparoscopy at sites without any former adhesions. Reformed adhesions are adhesions that formed at the sites of adhesiolysis during the first laparoscopy [16].

Adhesions were graded using the Local Adhesion Barrier Scoring System (LABS) score, based on the modified version of the American Fertility Society score system [17]. The LABS is an integrated score system comprising the adhesion's morphology and extend of the site covered with adhesions (Table 1). The LABS score differs from the modified version of the American Fertility Society score system; adhesions are scored at a lower number of sites that are more specific to gynecologic surgery. Adhesions were systematically evaluated for incidence and LABS score at eight sites: both left and right tubes, ovaries and pelvic sidewall and the anterior and posterior uterus. For each patient, the total LABS score was calculated as the mean of LABS scores at these eight separate locations.

Table 1 Local Adhesion Barrier Scoring (LABS) system

LABS adhesion score		
Tenacity	Extend	Score
None	None (0% covered)	0
Mild	Localized (<33% covered))	1
Mild	Moderate (33–67% covered)	2
Mild	Extensive (>67% covered)	4
Severe	Localized (<33% covered))	4
Severe	Moderate (33–67% covered)	8
Severe	Extensive (>67% covered)	16

Safety aspects

All patients were treated in day care. Postoperatively, patients were controlled for temperature, pain, hemodynamic changes and signs of bleeding in the recovery area.

Outcomes

The primary outcome for this pilot study was the number of patients with de novo adhesions. Secondary outcomes were change in the number of sites covered with adhesions and change in LABS adhesion score.

The number of patients with any adhesions is the most preferable outcome of adhesion prevention studies. However, as the sample size of this pilot study would be inadequate to provide in sufficient power on this outcome, we addressed this outcome in meta-analysis of systematically searched studies on PEG adhesion barrier.

Power analysis

Based on animal studies, the incidence of de novo adhesions was estimated at 30% in the PEG group and 90% in the control group [10]. Fourteen patients in each arm of the study were needed to detect such difference with 80% power and 5% two-tailed significance threshold at 1:1 randomization. Accounting for loss to follow-up, a minimum of 30 patients were to be randomized.

Statistical analysis

All statistical tests performed were two-tailed with significance was determined at the 5% level. Unpaired *t*-test was used for the testing of continuous data and Fisher's exact test for dichotomous data. All statistical analyses were performed using SPSS 16.0.2 (SPSS inc., Chicago, ILL).

Meta-analysis

A comprehensive search of Pubmed and Embase search was performed on July 1, 2011 to identify papers published in peer-reviewed journals from RCTs in surgical or gynaecological patients for the intervention with PEG and outcome adhesions. In Pubmed, randomized trials were identified via the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (sensitivity- and precision-maximizing version) [18]. We selected randomized trials in Embase using the top performing search strategy (minimizing difference between sensitivity and specificity version) described by Wong et al. [19]. Relevant RCTs were searched for data on the number of patients with any adhesions. The incidence of adhesions was expressed in odds ratio (OR) for meta-analysis. A fixed-effects model was applied for meta-analysis. In the presence of significant heterogeneity, the random-effects model was applied. Heterogeneity was tested with Cochrane Q-test and I^2 test. An I^2 value $\geq$50% or P value <0.05 was considered significant. Meta- analysis was carried out using Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark).

End of study

The study was prematurely ended due to financial and organizational reasons. During the conduct of the study, the clinical trial insurance unexpectedly required a separate fee for both laparoscopic procedures in each patient.

Results

A total of 16 eligible patients gave informed consent. Fifteen underwent successful laparoscopic gynecological or fertility surgery and were randomized. One patient had severe pelvic adhesions that could not be lysed completely and was excluded before randomization. There were no significant differences between the PEG and control group at index laparoscopy in age, type of surgical procedure, history of prior surgery, Chlamydia serology and smoking status at baseline (Table 2). Adhesiolysis was performed in 14 patients.

At index laparoscopy, there was a non-significant trend towards more sites covered with adhesions (5.1±2.3 vs. 3±2.2; P=0.10) and higher LABS score (3.7±2.8 vs. 2.4±3.0; P=0.40) in the PEG group (Table 3). Time of surgery was comparable between the PEG and control group at index laparoscopy. Time period between initial and second look laparoscopies was similar for both groups: 27.9±11.5 days in the PEG group and 28.0±17.6 in the control group (P>0.99).

All 15 randomized patients underwent SLL. De novo adhesions were found in 0/9 patients in the PEG group (0%) compared to 4/6 (67%) of patients in the control group (P=0.01). Patients in the PEG group had a decrease in LABS score compared to an increase in the control group (−2.6±2.1 vs. 0.1±1.7; P=0.03). This decrease was most prominent at the ovaries and fallopian tubes sites. The change in the number of sites covered with adhesions was −2.4±2.0 for patients treated with PEG spray compared to 0.8±2.3 for control patients (P=0.01). There were no significant differences in the absolute incidence, sites covered with adhesions and LABS scores between the PEG group and controls at SLL (Table 4). There were no post- operative complications in both groups.

Although no significant differences were found in the incidence of adhesions at any of the specific sites at SLL,

Table 2 Baseline characteristics

	PEG	Control	*P* value
Number of randomized patients	9	6	
Age	30.1±5.7[a]	34.5±4.3[a]	0.12
Type of surgical procedures performed			
Adhesiolysis	8 (89%)	5 (83%)	>0.99
Salpingotomy/salpingectomy	4 (44%)	2 (33%)	>0.99
Cystectomy	2 (22%)	3 (50%)	0.33
Laparotomy	0/9 (0%)	0/6 (0%)	>0.99
Laparoscopy	5/9 (56%)	5/6 (83%)	0.58
Positive Chlamydia serology	4/9 (44%)	1/6(17%)	0.58
Smoker	1/9 (11%)	0/6 (0%)	>0.99
Completed SLL	9 (100%)	6 (100%)	>0.99

[a]Mean±SD

the effect of PEG appeared maximal at the ovaries. The incidence of adhesions around the ovaries was reduced between index laparoscopy and SLL in the PEG treated group by 33% and 44% for the right and left ovaries, respectively. On the contrary, a 17% and 33% increase in incidence of adhesions around the right and left ovaries, respectively, was seen in control patients.

Meta-analysis of adhesion incidence

A total of 85 papers from peer-reviewed journals were identified using the search strategy. Five papers were identified studying the efficacy of PEG on adhesion formation after peritoneal surgery in an RCT [11–14, 20]. The number of patients with any adhesions could be assessed from three papers investigating patients undergoing myomectomy [11, 13, 20]. One paper was excluded because it described an interim analysis and results from the completed study were described in another paper [11, 20]. Thus, two RCTs and the present study remained for meta-analysis. In all here studies a trend towards a lower overall incidence of adhesions was demonstrated in PEG treated patients. Pooled data, using a fixed effects model, showed a significant reduction of the incidence of adhesions with an OR of 0.27 (95% CI 0.11–0.67; P=0.005, Fig. 1).

Discussion and conclusion

From this study, PEG anti-adhesion barrier seems effective in the prevention of de novo adhesions in common gynecological laparoscopic procedures, but especially in fertility enhancing procedures. Furthermore, there was a significant difference in change of LABS score favoring patients treated with PEG adhesion barrier. Meta-analysis also showed a significant reduction in the total incidence of adhesions.

The PEG anti-adhesion barrier has a set of unique characteristics compared to other existing barriers. The

Table 3 Adhesions at initial laparoscopy

	PEG	Control	*P* value
Patients with any adhesion	8/9 (89%)	5/6 (83%)	>0.99
Adhesion sites	5.1±2.3[a]	3±2.2[a]	0.10
LABS score (mean)	3.7±2.8[a]	2.4±3.0[a]	0.44
• Left ovary	5.1±4.9	2.0±3.3	0.17
• Right ovary	5.8±6.0	4.0±6.2	0.59
• Left fallopian tube	6.4±5.8	2.0±3.3	0.08
• Right fallopian tube	6.2±5.7	3.5+6.3	0.42
• Left pelvic side wall	3.3±3.2	1.3±3.3	0.27
• Right pelvic side wall	1.6±2.8	4.3±6.5	0.36
• Anterior uterus	0.2±0.7	0.0±0.0	0.35
• Posterior uterus	1.2±1.7	2.7±2.1	0.19
Time of surgery (min)	151.9±29.5[a]	146.7±47.8[a]	0.82
Time to SLL (days)	27.9±11.5[a]	28.0±17.6[a]	>0.99

SLL second look laparscopy
[a]Mean±SD

Table 4 Adhesions at second look laparoscopy

Outcome	PEG	Control	*P* value
Patients with any adhesion	7/9 (78%)	6/6 (100%)	0.49
Patients with de novo adhesions	0/9 (0%)	4/6 (67%)	0.01
Adhesions (number of sites)	2.7±2.4[a]	3.8±1.7[a]	0.29
Δ Adhesions (number of sites)[a]	−2.4±2.0[a]	0.8±2.3[a]	0.01
LABS score (Mean)	1.2±1.3[a]	2.4±2.4[a]	0.29
• Left ovary	0.7±0.9	2.2±3.0	0.28
• Right ovary	2.9±5.2	5.5±6.4	0.43
• Left fallopian tube	2.2±3.3	1.7±1.4	0.66
• Right fallopian tube	2.3±2.8	2.8±6.5	0.86
• Left pelvic side wall	1.0±2.6	0.7±1.0	0.74
• Right pelvic side wall	0.0±0.0	4.0±6.7	0.20
• Anterior uterus	0.0±0.0	0.0±0.0	1.00
• Posterior uterus	0.3±0.5	2.5±3.1	0.15
Δ LABS score[b] (mean)	−2.6±2.1[a]	0.1±1.7[a]	0.03
• Left ovary	−4.4±5.1	0.2±2.2	0.03
• Right ovary	−2.9±4.8	1.5±5.3	0.13
• Left fallopian tube	−4.2±5.0	−0.3±4.0	0.12
• Right fallopian tube	−3.9±4.0	−0.7±1.2	0.05
• Left pelvic side wall	−2.3±2.8	−0.7±3.7	0.38
• Right pelvic side wall	−1.6±2.8	−0.3±0.8	0.24
• Anterior uterus	−0.2±0.7	0.0±0.0	0.35
• Posterior uterus	−0.9±1.5	−0.2±2.7	0.57

[a]Mean±SD

[b]Δ = difference between index laparoscopy and second look laparoscopy

formula of two liquid PEG precursors that rapidly polymerize into a solid hydrogel, allows the surgeon to laparoscopically apply a barrier with the characteristics of a site specific barrier and the ease of application of a liquid [12]. Most site specific barriers are solid membranes that are difficult to apply laparoscopically. Site specific adhesion barriers seem most efficacious against adhesion (re)formation as they remain on the exact place of application during mesothelial healing. In the study of Ferland et al. both uterine horns and opposing peritoneum in a porcine model were abraded. One side was randomly assigned to coverage with a 1- to 2-mm-thick layer of PEG adhesion barrier. The barrier remained in place, and at SLL a significantly lower incidence of adhesion was found at the treated sides, demonstrating that the PEG adhesion barrier acts as a site-specific adhesion barrier [10]. The methylene blue dye makes it easy to assess if an area is sufficiently covered with the PEG anti-adhesion barrier. PEG molecules polymerize without the need of an external energy source or excess heat production and the hydrogel remains intact for 5–6 days, which is long enough for peritoneal layers to heal [21]. When degrading, the hydrogel falls apart in water-soluble PEG molecules that are easily resorbed and cleared in the urine [22].

Although a small number of patients could be included in this trial, our findings support those of earlier studies demonstrating that PEG spray is a highly efficacious site specific barrier for laparoscopic use. The incidence of adhesions could be assessed from two previous RCTs in patients undergoing myomectomy [11, 13]. In the present study and the two RCTs, a trend towards a lower overall

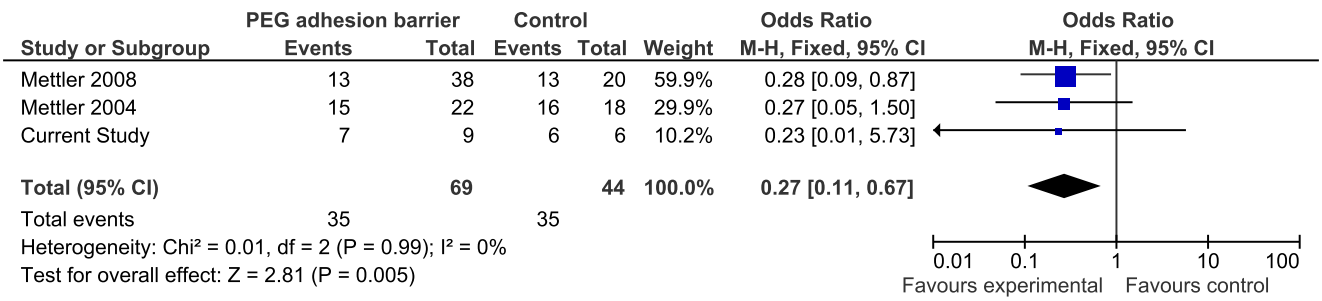

Fig. 1 Results from meta-analysis on the efficacy of PEG adhesion barrier reducing the total incidence of adhesions

incidence of adhesions was demonstrated in PEG treated patients. Pooled data showed a significant reduction of the incidence of adhesions in our meta-analysis. Complete adhesion prevention is of particular importance as it is the only means of providing a definitive protection against all adhesion related complications, such as infertility, ASBO and inadvertent enterotomies.

A limitation of this study is the analysis of adhesion prevention and not the clinical complications of adhesions, such as infertility or ASBO. Infertility as an endpoint is difficult to assess because failure to attain pregnancy is a multi-factorial endpoint. To assess the efficacy of adhesion barriers on fertility, a randomised trial is required in subfertile patients due to tubal pathology, which compares use of a barrier to no treatment after adhesiolysis and compares time to natural conception. Oxidized regenerating cellulose (Interceed®, Ethicon, Sommerville, NJ) is the only adhesion barrier that was proven to increase pregnancy rate in an RCT [23]. However, oxidized regenerating cellulose has limitations because it is difficult to handle laparoscopically and can cause adverse adhesiogenic effects in the presence of blood [24, 25]. Studies evaluating the efficacy of adhesion barriers in reducing the number of ASBO and enterotomies are rare. The incidence of these complications is relative low, thus a large number of patients is needed to demonstrate a significant effect. Modified sodium hyaluronic acid (HA) and carboxymethylcellulose (Seprafilm®; Genzyme Corporation, Cambridge, MA) reduced the number of ASBO requiring reoperation or found at autopsy by 45% in a study of 1,701 patients who underwent benign colorectal surgery [26]. This barrier has limitations because it cannot easily be applied at laparoscopy.

Change in adhesion score can be difficult to interpret as an outcome measure for adhesion prevention because the adhesion score at baseline influences the maximal effect. However, in our study, not only the size but also the direction of the effect differed between the groups. There was a marked decrease in LABS adhesion score in PEG treated group, while patients in the control group had a slight increase in adhesion score.

To study the efficacy of adhesion barriers by means of a second look procedure is becoming increasingly difficult. First, it is deemed more and more unethical to perform an invasive second procedure just for scientific purposes. Second, the benefit of SLL as part of fertility surgery is questionable. Today, women have more access to alternative treatment modalities to become pregnant such as in vitro fertilization [27]. Future adhesion prevention studies expectedly have to rely on non-invasive techniques to evaluate adhesion formation. For long, this has been considered impossible but recent studies show promising results of cine-MRI as a non-invasive diagnostic tool for the detection of adhesions [28]. More experience is needed to delineate the value of cine-MRI as an alternative to SLL in adhesion prevention studies.

Sprayable barriers that can be introduced via a laparoscopic trocar and handled with ease in the abdominal-pelvic cavity are of surplus value in the therapeutic arsenal of adhesion preventive agents. Clinical trials have demonstrated that laparoscopy only reduces the extend of adhesions but does not decrease the incidence of adhesions [29, 30]. Maximal efforts to prevent adhesion formation in fertility surgery should therefore comprise laparoscopy as well as an adhesion barrier. Although a large number of agents show adhesion reduction in animal models, only a few demonstrated such effects in RCT in humans [31–33]. PEG is one of a few barriers that has been evaluated in both gynecological and gastrointestinal patients and was found to be effective in both our study and previous RCTs [11, 13, 14, 20]. However, more research is needed to investigate the effect on adhesion related complications, such as ASBO and infertility.

Conflict of interest The study was investigator-initiated. Confluent Surgical Inc. (Waltham, MA) kindly provided the PEG adhesion barrier and paid the trial insurance fees of patients participating in this study. There were no further financial ties to Confluent Surgical Inc.

References

1. van Goor H (2007) Consequences and complications of peritoneal adhesions. Colorectal Dis 9(Suppl 2):25–34
2. Lower AM, Hawthorn RJ, Clark D et al (2004) Adhesion-related readmissions following gynaecological laparoscopy or laparotomy in Scotland: an epidemiological study of 24 046 patients. Hum Reprod 19:1877–1885
3. Montz FJ, Holschneider CH, Solh S et al (1994) Small bowel obstruction following radical hysterectomy: risk factors, incidence, and operative findings. Gynecol Oncol 53:114–120
4. Kaminski P, Gajewska M, Wielgos M et al (2006) The usefulness of laparoscopy and hysteroscopy in the diagnostics and treatment of infertility. Neuro Endocrinol Lett 27:813–817
5. Cates W, Farley TM, Rowe PJ (1985) Worldwide patterns of infertility: is Africa different? Lancet 2:596–598
6. Swank DJ, van Erp WF, Repelaer Van Driel OJ et al (2003) A prospective analysis of predictive factors on the results of laparoscopic adhesiolysis in patients with chronic abdominal pain. Surg Laparosc Endosc Percutan Tech 13:88–94
7. Mettler L, Alhujeily M (2007) Role of laparoscopy in identifying the clinical significance and cause of adhesions and chronic pelvic pain: a retrospective review at the Kiel School of Gynecological Endoscopy. JSLS 11:303–308
8. Van Der Krabben AA, Dijkstra FR, Nieuwenhuijzen M et al (2000) Morbidity and mortality of inadvertent enterotomy during adhesiotomy. Br J Surg 87:467–471
9. Dunn R, Lyman MD, Edelman PG et al (2001) Evaluation of the SprayGel adhesion barrier in the rat cecum abrasion and rabbit uterine horn adhesion models. Fertil Steril 75:411–416

10. Ferland R, Mulani D, Campbell PK (2001) Evaluation of a sprayable polyethylene glycol adhesion barrier in a porcine efficacy model. Hum Reprod 16:2718–2723
11. Mettler L, Audebert A, Lehmann-Willenbrock E et al (2004) A randomized, prospective, controlled, multicenter clinical trial of a sprayable, site-specific adhesion barrier system in patients undergoing myomectomy. Fertil Steril 82:398–404
12. Johns DA, Ferland R, Dunn R (2003) Initial feasibility study of a sprayable hydrogel adhesion barrier system in patients undergoing laparoscopic ovarian surgery. J Am Assoc Gynecol Laparosc 10:334–338
13. Mettler L, Hucke J, Bojahr B et al (2008) A safety and efficacy study of a resorbable hydrogel for reduction of post-operative adhesions following myomectomy. Hum Reprod 23:1093–1100
14. Tjandra JJ, Chan MK (2008) A sprayable hydrogel adhesion barrier facilitates closure of defunctioning loop ileostomy: a randomized trial. Dis Colon Rectum 51:956–960
15. Revised American Society for Reproductive Medicine (1997) Classification of endometriosis: 1996. Fertil Steril 67:817–821
16. Diamond MP, Wexner SD, diZereg GS et al (2010) Adhesion prevention and reduction: current status and future recommendations of a multinational interdisciplinary consensus conference. Surg Innov 17:183–188
17. American Fertility Society (1988) The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions. Fertil Steril 49:944–955
18. Higgins J, Green S (2009) Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration
19. Wong SS, Wilczynski NL, Haynes RB (2006) Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 94:451–455
20. Mettler L, Audebert A, Lehmann-Willenbrock E et al (2003) Prospective clinical trial of SprayGel as a barrier to adhesion formation: an interim analysis. J Am Assoc Gynecol Laparosc 10:339–344
21. Reijnen MM, Bleichrodt RP, van Goor H (2003) Pathophysiology of intra-abdominal adhesion and abscess formation, and the effect of hyaluronan. Br J Surg 90:533–541
22. Yamaoka T, Tabata Y, Ikada Y (1994) Distribution and tissue uptake of poly(ethylene glycol) with different molecular weights after intravenous administration to mice. J Pharm Sci 83:601–606
23. Sawada T, Nishizawa H, Nishio E et al (2000) Postoperative adhesion prevention with an oxidized regenerated cellulose adhesion barrier in infertile women. J Reprod Med 45:387–389
24. Wiseman DM, Gottlick-Iarkowski L, Kamp L (1999) Effect of different barriers of oxidized regenerated cellulose (ORC) on cecal and sidewall adhesions in the presence and absence of bleeding. J Invest Surg 12:141–146
25. Wiseman DM, Gottlick LE, Diamond MP (1992) Effect of thrombin-induced hemostasis on the efficacy of an absorbable adhesion barrier. J Reprod Med 37:766–770
26. Fazio VW, Cohen Z, Fleshman JW et al (2006) Reduction in adhesive small-bowel obstruction by Seprafilm adhesion barrier after intestinal resection. Dis Colon Rectum 49:1–11
27. Duffy JM, Johnson N, Ahmad G et al (2009) Postoperative procedures for improving fertility following pelvic reproductive surgery. Cochrane Database Syst Rev CD001897
28. Lienemann A, Sprenger D, Steitz HO et al (2000) Detection and mapping of intraabdominal adhesions by using functional cine MR imaging: preliminary results. Radiology 217:421–425
29. Lundorff P, Hahlin M, Kallfelt B et al (1991) Adhesion formation after laparoscopic surgery in tubal pregnancy: a randomized trial versus laparotomy. Fertil Steril 55:911–915
30. Audebert AJ, Gomel V (2000) Role of microlaparoscopy in the diagnosis of peritoneal and visceral adhesions and in the prevention of bowel injury associated with blind trocar insertion. Fertil Steril 73:631–635
31. Metwally M, Watson A, Lilford R et al (2006) Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. Cochrane Database Syst Rev CD001298
32. Kumar S, Wong PF, Leaper DJ (2009) Intra-peritoneal prophylactic agents for preventing adhesions and adhesive intestinal obstruction after non-gynaecological abdominal surgery. Cochrane Database Syst Rev CD005080
33. Ahmad G, Duffy JM, Farquhar C et al (2008) Barrier agents for adhesion prevention after gynaecological surgery. Cochrane Database Syst Rev CD000475